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ASTRUM-005: Updated results of first-line serplulimab versus placebo combined with chemotherapy in extensive-stage small-cell lung cancer

An international, multicentre, phase 3 study

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DECLARATION OF INTERESTS

No relationship with companies to declare.

Background

Anti-PD-L1 plus chemotherapy is now the first-line standard of care for ES-SCLC; however, OS benefits are still modest (improvement in median OS, 2.0–2.5 months).[1–3]

Serplulimab is the first PD-1 inhibitor demonstrating a significant OS benefit when combined with chemotherapy in patients with ES-SCLC.[4]

At the interim analysis of ASTRUM-005, median OS was significantly longer with serplulimab plus chemotherapy than placebo plus chemotherapy (15.4 vs. 10.9 months, HR, 0.63 [95% CI, 0.49–0.82]; p<0.001).[4]

Here we report the results from an updated analysis of ASTRUM-005 (data cut-off date, 13 June 2022) after a median follow-up of 19.8 months.

1. Liu SV, *et al. J Clin Oncol*. 2021;39(6):619–630. 2. Paz-Ares L, *et al. ESMO Open*. 2022;7(2):100408. 3. Wang J, *et al. Lancet Oncol*. 2022;23(6):739–747. 4. Cheng Y, *et al. JAMA*. 2022;328(12):1223–1232.
CI, confidence interval; **chemotherapy**, etoposide-platinum; **ES**, extensive stage; **HR**, hazard ratio, **PD-L1**, programmed death ligand-1; **PD-1**, programmed death-1; **SCLC**, small-cell lung cancer.

Interim Results of ASTRUM-005 (NCT04063163)

- Serplulimab plus chemotherapy significantly improved OS compared with placebo plus chemotherapy in previously untreated ES-SCLC patients. PFS was also prolonged with the addition of serplulimab.

Results from interim analysis (data cut-off date, 22 October 2021)[1]		
Median duration of follow-up	Month	12.3
Treatment ongoing	n (%)	97 (24.9) vs. 23 (11.7)
OS	Events, n (%)	146 (37.5) vs. 100 (51.0)
	HR (95% CI), p-value	0.63 (0.49–0.82), p<0.001
PFS*	Events, n (%)	223 (57.3) vs. 151 (77.0)
	HR (95% CI)	0.48 (0.38–0.59)

n=389 in serplulimab-chemotherapy group and n=196 in placebo-chemotherapy group.
**PFS assessed by IRRC per RECIST v1.1.*

1. Cheng Y, *et al. JAMA*. 2022;328(12):1223–1232.

Chemotherapy, etoposide-platinum; **CI**, confidence interval; **ES**, extensive stage; **HR**, hazard ratio; **IRRC**, independent radiology review committee; **OS**, overall survival; **PFS**, progression-free survival; **RECIST**, Response Evaluation Criteria in Solid Tumors; **SCLC**, small-cell lung cancer.

Study Design

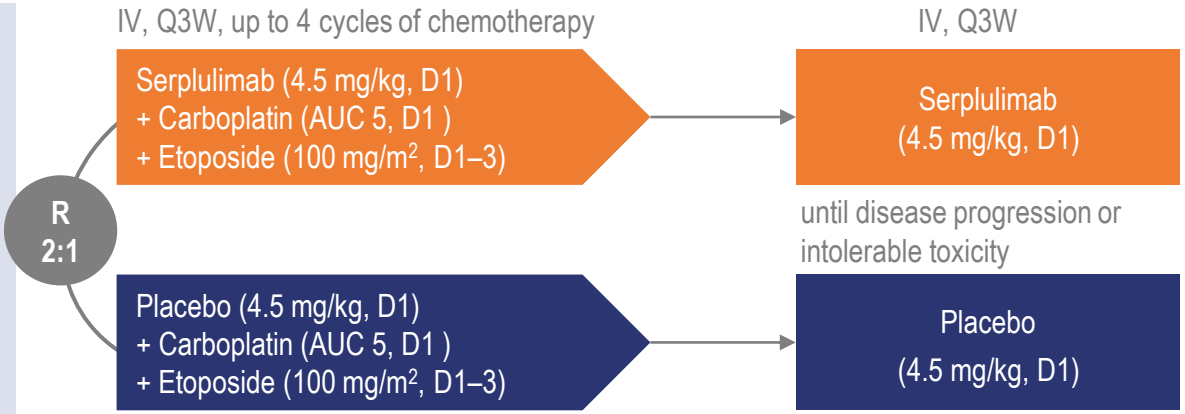
A randomised, double-blind, placebo-controlled, global phase 3 trial (NCT04063163)

Patients

- Histologically/cytologically diagnosed with ES-SCLC
- No prior systemic therapy for ES-SCLC
- At least one measurable lesion
- ECOG PS 0/1

Stratification factor

- PD-L1 expression (negative: TPS <1%, positive: TPS ≥1%, or NA)
- Brain metastases (yes vs. no)
- Age (<65 vs. ≥65 years)



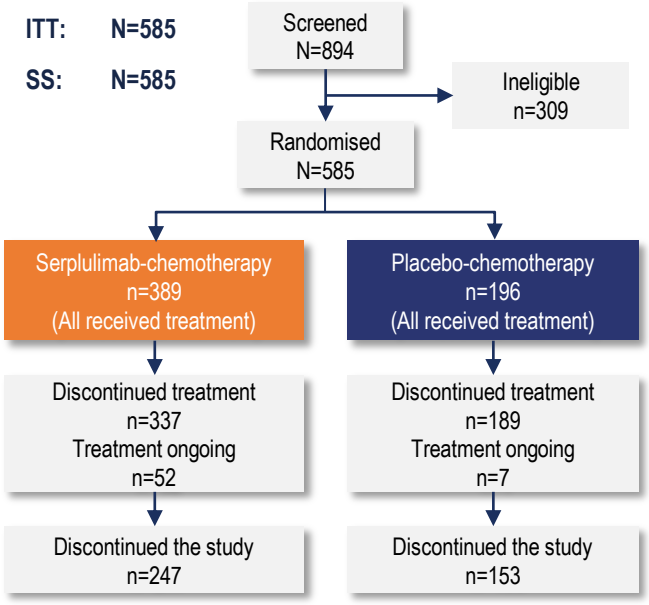
- **Primary endpoint:** OS
- **Key secondary endpoints:** PFS, ORR, DOR, and safety

Updated

- **OS in ITT and in patient subgroups (including race)**
- **PFS in ITT and in race subgroups; ORR and DOR in ITT**
- **Safety**

AUC, area under curve; **chemotherapy**, etoposide-platinum; **D**, Day; **DOR**, duration of response; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **ES-SCLC**, extensive-stage small-cell lung cancer; **ITT**, intention to treat; **IV**, intravenous infusion; **NA,** not available; **ORR**, objective response rate; **OS**, overall survival; **PFS**, progression-free survival; **PD-L1**, programmed death ligand-1; **Q3W**, every 3 weeks; **R**, randomisation; **TPS**, tumour proportion score.

Patient Disposition and Baseline Characteristics



Median duration of follow-up: 19.8 months

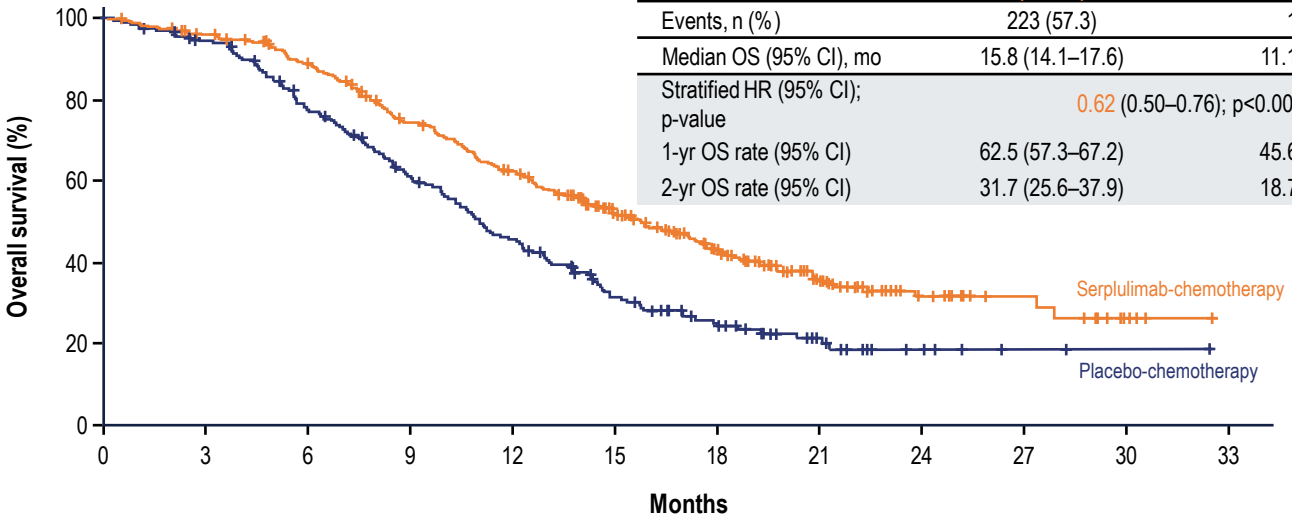
Characteristics	Serplulimab-chemotherapy (n=389)	Placebo-chemotherapy (n=196)
Age, median (range), years	63 (28–76)	62 (31–83)
≥65, n (%)	154 (39.6)	77 (39.3)
Male, n (%)	317 (81.5)	164 (83.7)
Asian, n (%)	262 (67.4)	139 (70.9)
Smoking status, n (%)		
Current	102 (26.2)	48 (24.5)
Former	206 (53.0)	113 (57.7)
Never	81 (20.8)	35 (17.9)
SOD of target lesion, median (range), mm	117.7 (13.8–323.7)	120.5 (14.5–269.6)
ECOG PS 1, n (%)	318 (81.7)	164 (83.7)
Prior anti-cancer therapy, n (%)		
Chemotherapy[a]	9 (2.3)	3 (1.5)
Other[b]	1 (0.3)	2 (1.0)
PD-L1 expression levels, n (%)		
Positive, TPS ≥1%	62/379 (16.4)	34/186 (18.3)
Negative, TPS <1%	317/379 (83.6)	152/186 (81.7)
PD-L1 expression levels, n (%)		
Positive, CPS ≥1	201/376 (53.5)	96/186 (51.6)
Negative, CPS <1	175/376 (46.5)	90/186 (48.4)
Brain metastases, n (%)	50 (12.9)	28 (14.3)
Liver metastases, n (%)	99 (25.4)	51 (26.0)

[a] 11 patients received prior treatment for limited-stage SCLC (treatment-free interval ≥6 months). 1 patient received prior treatment for gastric cancer (>5 years ago). [b] Other treatments included herbal or Traditional Chinese Medicine and immunostimulant lentinan.

Chemotherapy, etoposide-platinum; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **ITT**, intention to treat; **PD-L1**, programmed death ligand-1; **SCLC**, small-cell lung cancer; **SOD**, sum of diameters; **SS**, safety set; **TPS**, tumour proportion score.

Updated OS in ITT

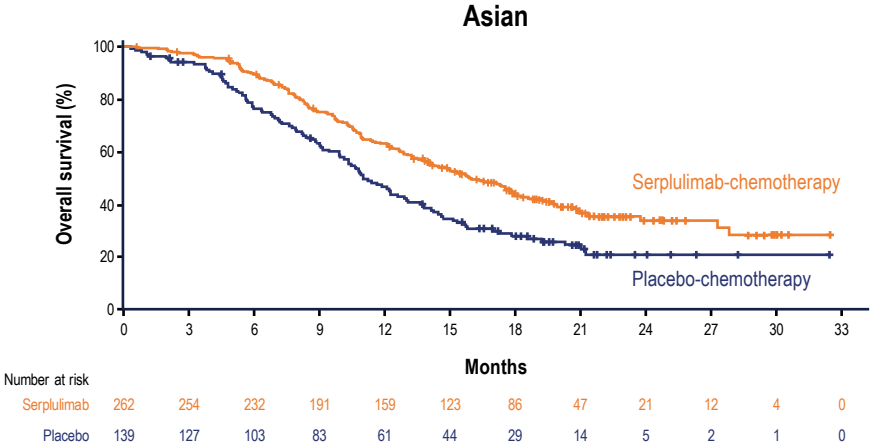
	Serplulimab-chemotherapy (n=389)	Placebo-chemotherapy (n=196)
Events, n (%)	223 (57.3)	140 (71.4)
Median OS (95% CI), mo	15.8 (14.1–17.6)	11.1 (10.0–12.4)
Stratified HR (95% CI); p-value	0.62 (0.50–0.76); p<0.001	
1-yr OS rate (95% CI)	62.5 (57.3–67.2)	45.6 (38.3–52.6)
2-yr OS rate (95% CI)	31.7 (25.6–37.9)	18.7 (12.5–25.9)

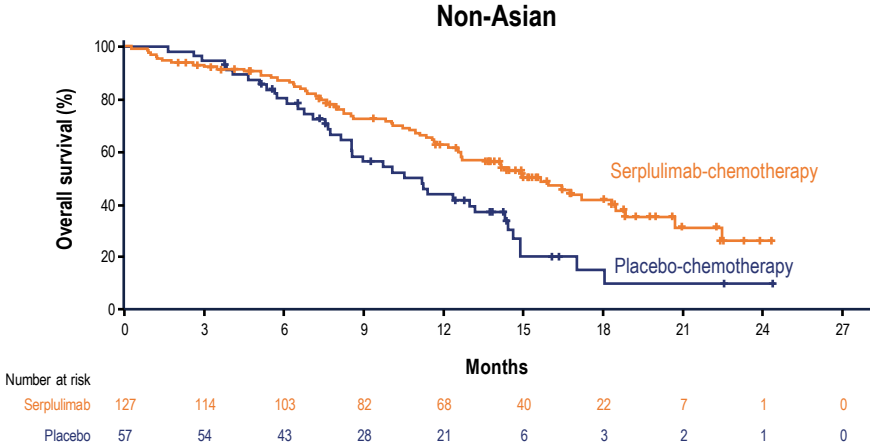


Number at risk												
Serplulimab	389	368	335	273	227	163	108	54	22	12	4	0
Placebo	196	181	146	111	82	50	32	16	6	2	1	0

Chemotherapy, etoposide-platinum; **CI**, confidence interval; **HR**, hazard ratio; **ITT**, intention to treat; **mo**, month; **OS**, overall survival; **yr**, year.

OS in Asian vs. Non-Asian





	Serplulimab-chemotherapy (n=262)	Placebo-chemotherapy (n=139)
Events, n (%)	157 (59.9)	101 (72.7)
Median OS (95% CI), mo	15.9 (13.9–17.9)	11.1 (10.0–12.9)
Unstratified HR (95% CI); p-value	0.63 (0.49–0.81); p<0.001	
1-yr OS rate (95% CI)	62.5 (56.3–68.1)	46.2 (37.5–54.4)
2-yr OS rate (95% CI)	33.1 (26.3–40.1)	20.2 (13.0–28.7)

	Serplulimab-chemotherapy (n=127)	Placebo-chemotherapy (n=57)
Events, n (%)	66 (52.0)	39 (68.4)
Median OS (95% CI), mo	15.6 (12.6–18.5)	11.2 (8.5–14.3)
Unstratified HR (95% CI); p-value	0.56 (0.37–0.83); p=0.004	
1-yr OS rate (95% CI)	62.6 (53.1–70.7)	44.0 (30.1–57.0)
2-yr OS rate (95% CI)	26.3 (13.7–40.7)	10.2 (2.2–25.6)

Chemotherapy, etoposide-platinum; **CI**, confidence interval; **HR**, hazard ratio; **mo**, month; **OS**, overall survival; **yr**, year.

Updated OS in Subgroups

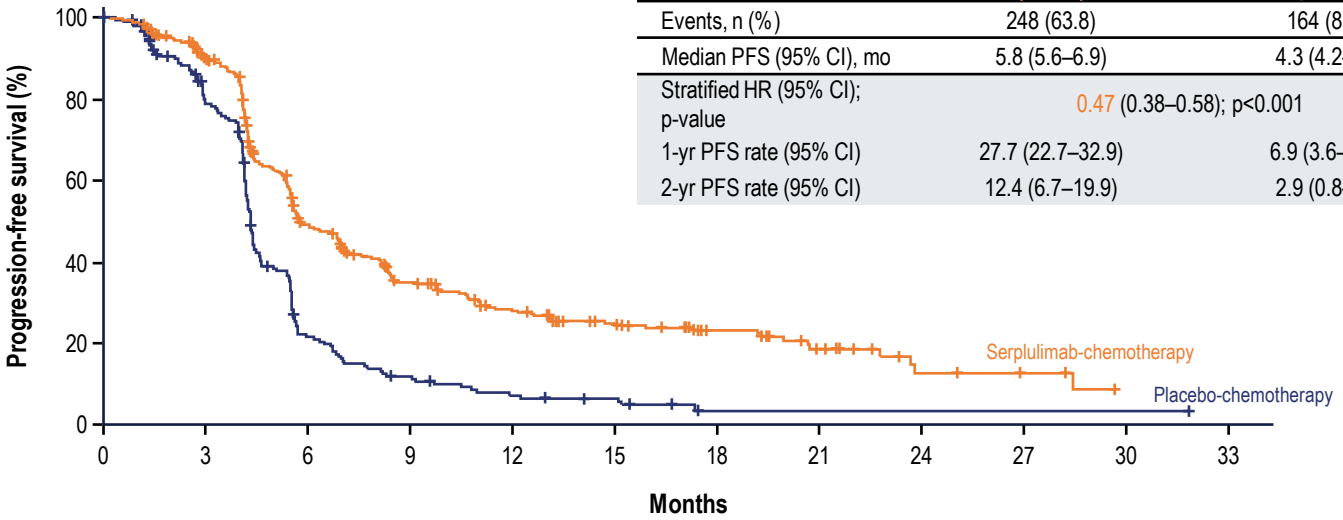
Subgroup	Serplulimab-chemotherapy (events/patients)	Placebo-chemotherapy (events/patients)	HR* (95% CI)
Age			
<65 years	129/235	86/119	0.56 (0.42, 0.73)
≥65 years	94/154	54/77	0.69 (0.50, 0.97)
Sex			
Male	182/317	119/164	0.61 (0.49, 0.77)
Female	41/72	21/32	0.65 (0.38, 1.10)
Race			
Asian	157/262	101/139	0.63 (0.49, 0.81)
Non-Asian	66/127	39/57	0.56 (0.37, 0.83)
Baseline ECOG performance status			
0	33/71	16/32	0.60 (0.33, 1.09)
1	190/318	124/164	0.63 (0.50, 0.79)
Smoking history			
Never	51/81	23/35	0.79 (0.48, 1.30)
Current	51/102	37/48	0.49 (0.32, 0.75)
Former	121/206	80/113	0.61 (0.46, 0.82)
Brain metastases			
No	188/339	119/168	0.60 (0.48, 0.75)
Yes	35/50	21/28	0.73 (0.42, 1.25)
Liver metastases			
No	152/290	96/145	0.62 (0.48, 0.80)
Yes	71/99	44/51	0.58 (0.40, 0.84)
PD-L1 expression level			
TPS <1%	187/317	112/152	0.61 (0.48, 0.77)
TPS ≥1%	31/62	19/34	0.69 (0.39, 1.23)
Not evaluable or not available	5/10	9/10	0.31 (0.09, 1.03)
PD-L1 expression level			
CPS <1	110/175	66/90	0.65 (0.48, 0.88)
CPS ≥1	106/201	65/96	0.60 (0.44, 0.82)
Not evaluable or not available	7/13	9/10	0.49 (0.17, 1.41)
Overall	223/389	140/196	0.62 (0.50, 0.76)

* The HRs were not stratified for the patient subgroups and was stratified for the overall population.

CI, confidence interval; **CPS**, combined positive score; **ECOG**, Eastern Cooperative Oncology Group; **chemotherapy**, etoposide-platinum; **HR**, hazard ratio; mo, month; **OS**, overall survival; **PD-L1**, programmed death ligand-1; **TPS**, tumour proportion score.

Updated PFS by IRRC per RECIST v1.1

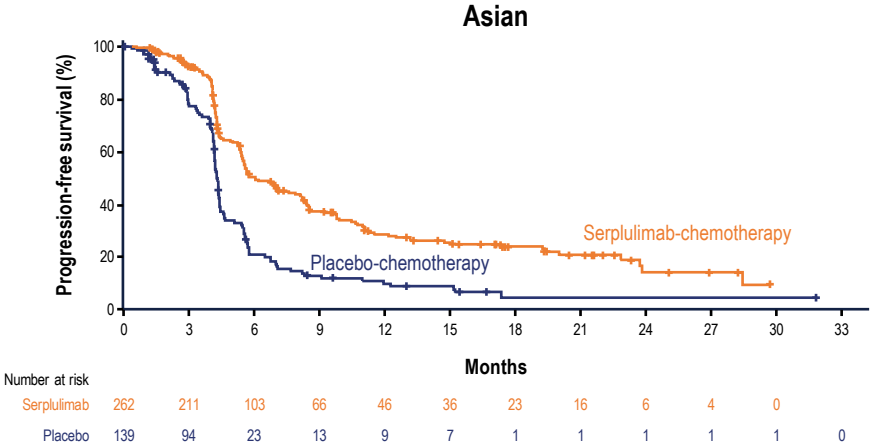
	Serplulimab-chemotherapy (n=389)	Placebo-chemotherapy (n=196)
Events, n (%)	248 (63.8)	164 (83.7)
Median PFS (95% CI), mo	5.8 (5.6–6.9)	4.3 (4.2–4.4)
Stratified HR (95% CI); p-value	0.47 (0.38–0.58); p<0.001	
1-yr PFS rate (95% CI)	27.7 (22.7–32.9)	6.9 (3.6–11.5)
2-yr PFS rate (95% CI)	12.4 (6.7–19.9)	2.9 (0.8–7.6)

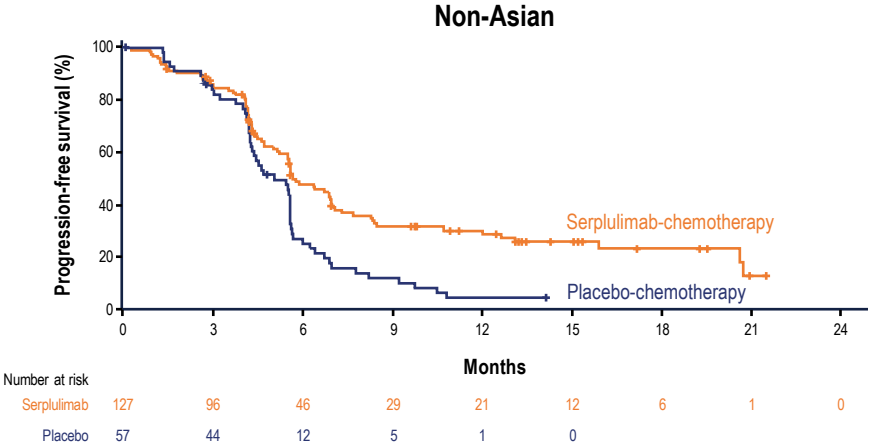


Number at risk												
Serplulimab	389	307	149	95	67	48	29	17	6	4	0	
Placebo	196	138	35	18	10	7	1	1	1	1	1	0

Chemotherapy, etoposide-platinum; **CI**, confidence interval; **HR**, hazard ratio; **IRRC**, independent radiology review committee; **mo**, month; **PFS**, progression-free survival; **RECIST**, Response Evaluation Criteria in Solid Tumors; **yr**, year.

PFS by IRRC per RECIST v1.1 in Asian vs. Non-Asian





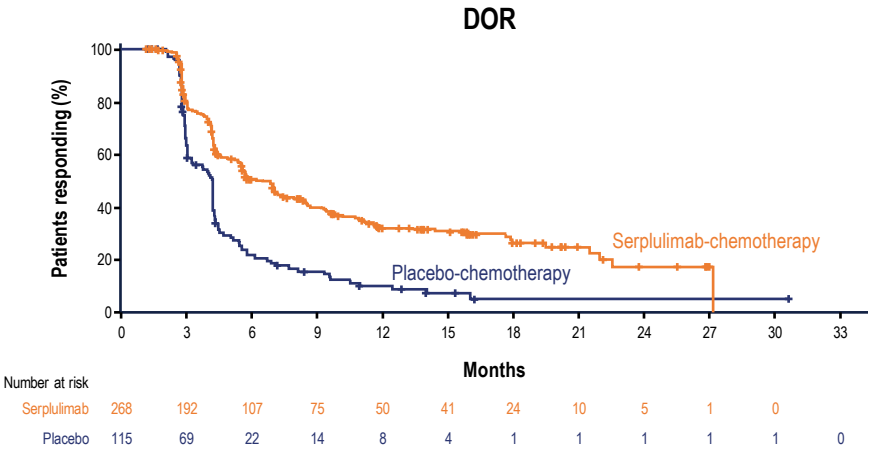
	Serplulimab-chemotherapy (n=262)	Placebo-chemotherapy (n=139)
Events, n (%)	165 (63.0)	112 (80.6)
Median PFS (95% CI), mo	6.1 (5.5–8.1)	4.3 (4.2–4.4)
Unstratified HR (95% CI); p-value	0.47 (0.37–0.61); p<0.001	
1-yr PFS rate (95% CI)	28.2 (22.0–34.7)	9.4 (4.9–15.7)
2-yr PFS rate (95% CI)	13.7 (7.3–22.1)	4.0 (1.0–10.2)

	Serplulimab-chemotherapy (n=127)	Placebo-chemotherapy (n=57)
Events, n (%)	83 (65.4)	52 (91.2)
Median PFS (95% CI), mo	5.7 (5.1–6.9)	5.0 (4.2–5.6)
Unstratified HR (95% CI); p-value	0.53 (0.37–0.76); p<0.001	
1-yr PFS rate (95% CI)	26.5 (18.3–35.5)	1.9 (0.2–8.9)
2-yr PFS rate (95% CI)	NA	NA

Chemotherapy, etoposide-platinum; **CI**, confidence interval; **HR**, hazard ratio; **IRRC**, independent radiology review committee; **mo**, month; **NA**, not available; **PFS**, progression-free survival; **RECIST**, Response Evaluation Criteria in Solid Tumors; **yr**, year.

Updated Tumour Response by IRRC per RECIST v1.1

	Serplulimab-chemotherapy (n=389)	Placebo-chemotherapy (n=196)
Confirmed ORR, n (%) [95% CI]	268 (68.9) [64.0–73.5]	115 (58.7) [51.4–65.6]
Best overall response, n (%)		
CR	6 (1.5)	0
PR	262 (67.4)	115 (58.7)
SD	94 (24.2)	60 (30.6)
PD	9 (2.3)	11 (5.6)
NE or missing	18 (4.6)	10 (5.1)
Median DOR (95% CI), mo	6.5 (5.5–7.5)	4.2 (3.1–4.2)
Stratified HR (95% CI); p-value	0.45 (0.35–0.59); p<0.001	

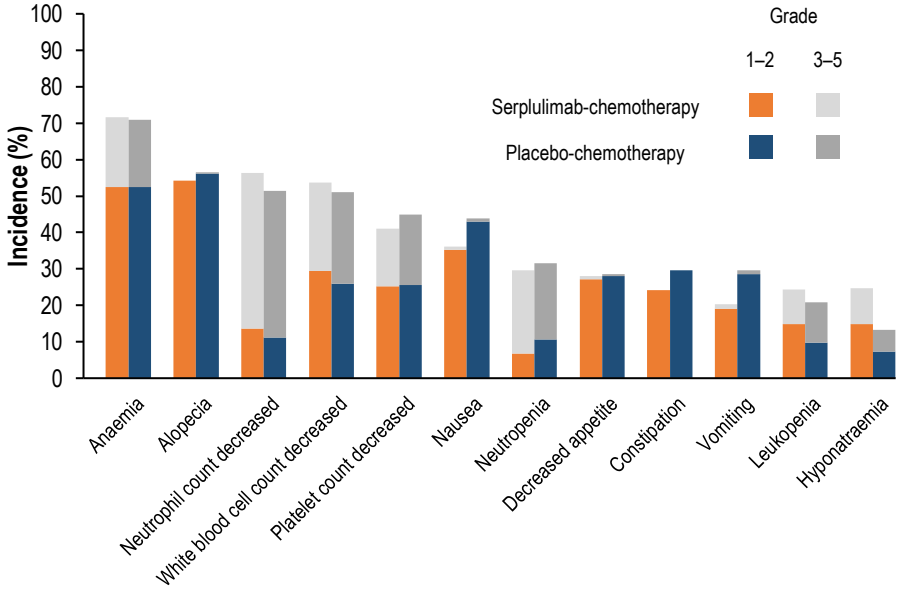


Chemotherapy, etoposide-platinum; **CI**, confidence interval; **CR**, complete response; **DOR**, duration of response; **IRRC**, independent radiological review committee; **mo**, month; **NE**, not evaluable; **ORR**, objective response rate; **PD**, progressive disease; **PR**, partial response; **RECIST**, Response Evaluation Criteria in Solid Tumors; **SD**, stable disease.

Updated Safety

An overview of TEAEs

	Serplulimab-chemotherapy (n=389)	Placebo-chemotherapy (n=196)
TEAEs, n (%)	373 (95.9)	191 (97.4)
CTCAE grade ≥3	324 (83.3)	160 (81.6)
SAEs	146 (37.5)	71 (36.2)
AESIs		
IRRs	7 (1.8)	1 (0.5)
irAEs	147 (37.8)	38 (19.4)
TEAEs related to serplulimab/placebo, n (%)	273 (70.2)	113 (57.7)
CTCAE grade ≥3	133 (34.2)	57 (29.1)
Leading to treatment discontinuation	23 (5.9)	10 (5.1)
Leading to death	5 (1.3)	1 (0.5)



TEAEs occurring in ≥20% patients in any group are shown.

AESI, adverse event of special interest; **chemotherapy**, etoposide-platinum; **CTCAE**, Common Terminology Criteria for Adverse Events; **irAE**, immune-related adverse event; **IRR**, infusion-related reaction; **SAE**, serious adverse event; **TEAE**, treatment-emergent adverse event.

Conclusions

In the updated analysis, serplulimab plus chemotherapy continued to provide benefits in OS, PFS, ORR, and DOR compared with placebo plus chemotherapy.

- Median OS: 15.8 vs. 11.1 months; HR, 0.62; p<0.001.
- Median PFS by IRRC per RECIST v1.1: 5.8 vs. 4.3 months; HR, 0.47; p<0.001.
- ORR: 68.9% vs. 58.7%; median DOR: 6.5 vs. 4.2 months (HR, 0.45) as assessed by IRRC per RECIST v1.1.
- The improved OS with serplulimab plus chemotherapy was observed across subgroups, including Asian and non-Asian.

The safety profile was similar between the two groups and consistent with that previously observed.

The Orphan-Drug Designation of serplulimab in SCLC has been granted by FDA. Additionally, the NDA of serplulimab in ES-SCLC is under review by NMPA.

Chemotherapy, etoposide-platinum; **DOR**, duration of response; **ES-SCLC**, extensive-stage small-cell lung cancer; **FDA**, United States Food and Drug Administration; **HR**, hazard ratio; **IRRC**, independent radiology review committee; **NDA**, new drug application; **NMPA**, National Medical Products Administration; **ORR**, objective response rate; **OS**, overall survival; **PFS**, progression-free survival; **RECIST**, Response Evaluation Criteria in Solid Tumors.

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